IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Cheng Hwang et al.	Art Unit	: 1611
Serial No.	: 10/721,118	Examiner	: Gina C Yu
Filed	: November 25, 2003	Conf. No.	: 6141

Title : REDUCTION OF HAIR GROWTH

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL FROM ACTION MAILED JUNE 11, 2010

(1) Real Party in Interest

The real party in interest is The Gillette Company, Prudential Tower Building, Boston, Massachusetts. The Gillette Company is owned by The Procter & Gamble Company.

(2) Related Appeals and Interferences

There are no related appeals or interferences.

(3) Status of Claims

Claims 1, 2, 4, 8 and 29-45 are examined in the Office Action mailed June 11, 2010.

Claims 1, 2, 4 and 29-45 are rejected.

Claim 8 has allowable subject matter and would be allowed if re-written to include all limitations of the base claim and intervening claims.

Claim 3 is cancelled.

Claims 5-7, 9-28 and 46 are withdrawn.

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: October 26, 2010

(4) Status of Amendments

No amendments have been submitted after the Office Action mailed June 11, 2010, and no amendments are pending.

(5) Summary of Claimed Subject Matter

Applicants have discovered that activators ("agonists") of a cell surface feature known as the prostaglandin DP-receptor (specification at page 3, line 27) can be applied to an area of mammalian skin to reduce hair growth (specification at page 2, line 2 under "Summary"). Claim 1 reads as follows:

1. A method of reducing mammalian hair growth which comprises

selecting an area of skin from which reduced hair growth is desired; and

applying to said area of skin a dermatologically acceptable composition comprising an agonist of prostaglandin DP-receptor in an amount effective to reduce hair growth.

(6) Grounds of Rejection to be Reviewed on Appeal

I. Claims 1, 2, 4 and 29-45 are rejected as obvious from a combination of two references:

- US2003/0220374 "Needleman"; and
- US 6,004,751 "Rosenfield".

II. Claims 1, 2, 4, 7[1] and 29-45 are rejected under 35 U.S.C. §112 ¶1 as not broadly enabled by the specification as filed.

These rejections are made in a non-final rejection mailed June 11, 2010. The rejections are ripe for appeal under 37 CFR § 41.31 because the claims have now rejected four times: a) in a non-final action mailed October 29, 2007; b) in a final rejection mailed September 16, 2008; c) in an advisory action mailed December 12, 2008; and d) in the instant June 11, 2010 action which withdrew all the previous rejections based on Applicants' Brief filed June 24, 2009 and then made the rejections now under appeal. No Examiner's Answer was filed to that brief.

[1] Claim 7 is withdrawn; clarification is requested.

(7) Argument

We discuss each of the two pending rejections after some brief background.

I. Background

As noted, claim 1 features methods of reducing hair growth by topically applying an agonist of a cell structure known as the DP-receptor. To understand this appeal, it is important to understand that the **DP receptor** is an entirely **different structure from** the members of a class of receptors known as PPAR receptors, such as **the PPAR-γ receptor**.

The DP receptor and the PPAR-γ receptor are different proteins encoded by different genes. The **gene sequences** and **protein sequences** are **different**. The **locations of the genes** are **different**.[2] The **locations** of the receptors **in the cell** are **different**. The DP receptor of the claims occurs on the outer cell membrane and it responds to its natural activator, PGD_2 (prostaglandin D2 ligand), initiating a number of intra-cellular events. The PPAR receptor family studied in the prior art controls gene transcription and occurs within the cell's nuclear membrane.

There is no evidence of record that PPAR receptors respond to the DP receptor activator, PGD_2.

In sum, no prior art equates PPAR-γ with the DP receptor. No one skilled in the art would confuse or equate the two structures. They are different.

We do not understand the Office to disagree that the structures are different. The most the Office concludes is that the two are "correlated", or at least the Office disputes that there is no correlation between them (June 11, 2010 Action at page 8, last two lines).[3] We review this key point below.

---

[2] These differences should not be in question. The gene encoding the human PPAR-γ receptor is located on chromosome 3, location 3p25. Both the sequence of the gene and the protein sequence of the PPAR-γ receptor are known. See Gene Bank accession number X90563 and HGNC number 9236.

The gene encoding the human DP receptor is located on chromosome 14, location: 14q22.1. Both the sequence of the gene and the protein sequence of the DP receptor are known. See GenBank accession number U31332 and HGNC ID number 9591. See also US 5,958,723.

[3] The Office says (page 8, lines 21-22), "...applicant's assertion that there is no correlation between PPAR family and prostaglandin DP receptor agonists is erroneous."

The application lists a large number of DP receptor agonists and provides data from experiments using those agonists topically to inhibit hair growth. See for example page 4 line 15 through page 5 (above the line-numbering) and see the experiments at pages 12-13, Tables III IV and V). See the discussion below regarding additional DP receptor agonists taught in the specification.

With that background we look at the rejections.

II. The claims are not obvious from the combined Needleman and Rosenfield teachings

A. The factual predicates for the obvious rejection have no support from, and are contradicted by, facts in the record.

The first step in the obviousness rejection is the Office's reliance on Needleman as teaching that PPAR-γ agonists **as a class** treat excessive unwanted hair growth or hirsutism. See page 7, lines 9-12 of the Office Action,

> Needlemen [sic Needleman] discloses hirsutism can be treated by administering to the subject with [sic?] PPAR peroxisome proliferators-activated receptors (PPARs) - γ agonists in an effective dosage. **See p. 6, Table 2 [of Needleman]**, ciglitazone, danglitazone [sic darglitazone], englitazone, pioglitazone, roniglitzone [sic rosiglitazone], and troglitazone [Emphasis is added].

This is a critical step in the obviousness analysis, because it is the only mention in the cited art of treating unwanted hair growth. The fact is, however, that Needleman is not interested in, and provides no teaching about, treating unwanted hair growth. Needleman most certainly does not teach that **PPAR-γ agonists as a class** treat hirsutism.

What then does the Office's citation to Needleman's Table 2 mean?[4]

Needleman is interested in PPAR-γ agonists for reasons that have nothing to do with treating hirsutism. The medical indications of concern to Needleman are listed in paragraph [0021] on page 3,

> [T]he present invention is directed to a novel method for the prevention, treatment, or inhibition of pain, inflammation, or inflammation-related disorder, or cancer, or Alzheimer's disease, or cardiovascular disease or disorder in a subject in need of such treatment, prevention, or inhibition, the method comprising treating the subject

[4] Table 2 at pp. 6-7 of Needleman is the **only part of Needleman that the Office references**.

with a peroxisome proliferator activated receptor-7 [sic γ?] agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

Of course Needleman lists a significant number of known PPAR-γ agonists. and that is the function of Table 2 – to list of known PPAR-γ agonists to use for the above indications. Table 2 also includes **compound-by-compound** medical indications taught in other publications. Thus, a compound designated "BRL49653" is indicated for Alzheimer's disease and central nervous system injury. Other compounds are indicated for diabetes, Alzheimer's disease, central nervous system injury, failure to ovulate (anovulation), cancer, hyperandrogenism, uterine bleeding, anti-viral, atherosclerosis, obesity, hypoglycemia, and dyslipidemia. And, yes, some compounds are indicated to treat hirsutism.

In fact, the only place Needleman mentions hirsutism is in Table 2 and he mentions it there only with regard to a few specific listed PPAR-γ agonists, which are structurally related to the compound ciglitazone.[5] The compounds indicated for hirsutism are structurally related in that they are all thiazolidinediones. Table 2 also reports at least one thiazolidinedione (Ragaglitazar) that is not (insofar as the cited reference is concerned) indicated for hirsutism.

Not one non-thiazolidinedione PPAR-λ agonist is indicated (in Table 2) for hirsutism. In fact, the vast **majority of the known PPAR-γ agonists** listed in Table 2 are listed for a wide variety of indications, **but are NOT listed as indicated for hirsutism**.[6] Perhaps most telling is Needleman's teaching in Table 2 about PPAR-γ agonists "in general". See the last entry in the table "one or more PPARγ Agonists in general" which does **not list hirsutism as a medical indication for the class of compounds**.

What does all of this mean? It means that any attempt to generalize a teaching about treating hirsutism from Needleman's Table 2 is flawed. Not even all ciglitazone analogs treat hirsutism, and no other compound in Table 2 does.

---

[5] The listed ciglitazone analogs indicated for hirsutism are darglitazone, pioglitazone, rosiglitazone (BRL 49653 or 5-[[4-(2-methyl-2-pyridinylamio)ethoxy]phenyl]methyl]-2,4-thiazolidinedione) and troglitazone.

[6] Among the PPAR-γ agonists listed in Table 2 that are **NOT** shown to be indicated for hirsutism are: a) docosahexanenoic acid, b) prostaglandin J2; c) 15-deoxy-$\Delta^{12,14}$-prostaglandin J2, d) DRF2725 (Ragaglitazar), e) CS-011 (a sulfonamide), f) CI-1037, g) AD-5075, h) GW1929, i) AY-31627, j) MCC-555, k) JTT501, l) PD72953, m) L764406, n) WAY-120,744, p) G1262570X, p) GG570, q) indomethacin.

Most important, the Office does not (and could not) take the position that ciglitazone and the listed related compounds are DP receptor agonists. They are not. Not one of the compounds listed as treating hirsutism is a DP receptor agonist.[7]

So the Office has mischaracterized Needleman as a general teaching that PPAR-γ agonists as a category treat hirsutism. The fact is that Needleman has no such teaching. The very next paragraph of the office action (on page 7. lines 16-18) says as much.

> One would not immediately envisage using the claimed compound for treating hirsutism. However, Needleman teaches that (PPARs)-γ agonists are used to inhibit cell growth.

The Office provides no art that permits a conclusion that cell growth inhibitors are generally effective to control hair growth.

Of course the Office's treatment of Needleman's teachings about PPAR agonists is only the beginning of the analysis because, as we have seen, the PPAR-λ receptor is not the DP receptor featured in Applicants' claims.

The next step in the rejection, at pages 7 and 8 of the action, attempts to explain the **relevance of PPAR-γ agonists** disclosed in Needleman to claims that features **DP receptor agonists.** That rationale involves Rosenfield and is quoted below (page 7, line 19 through page 8, line 6), but it is far from clear how Rosenfield is relevant to treating unwanted hair growth by any means at all.

> Rosenfield teaches PDG_2 [a natural ligand for the DP receptor] is a major product of cyclooxygenase in a variety of tissues and cells and readily undergoes dehydration in vivo and in vitro to yield prostaglandins of the J_2 series (PGJ_2). [Rosenfield] teaches the members of the PGJ_2 series are known to exhibit **inhibition of cell cycle progression, suppression of viral replication**, induction of **heat shock protein expression** and **stimulation of osteogenesis** See col. 12, lines 40-51... [emphasis is added].

Apparently all Rosenfield adds to Needleman is a list of cell functions that relate to the certain metabolites or metabolic precursors of PDG_2, the natural ligand for the DP receptor. In summing up Rosenfield's contribution, the Office goes back to cell cycle control, without citing any art or

---

[7] As an aside, the Office apparently recognizes this fact. A teaching in the art of a molecule that has both DP receptor agonist activity and hair growth reduction would anticipate the claim. No rejection is raised under 35 U.S.C. §102.

providing any analysis that permits a conclusion that cell growth inhibitors as a class are effective to control hair growth.

> **Although Needlemen [sic Needleman] and Rosenfield do not disclose PGJ_2 or its analogs specifically used in treating hirsutism or reducing hair growth**, [they] indicate that ... PGJ_2 and other PPAR-γ agonists have been known to inhibit cell cycle progression or growth.

In response to the three earlier rejections of the claims at issue, Applicant had pointed out that the rejection fails to make a connection between PPAR-γ agonists and DP receptor agonists or to provide any teaching at all about controlling hair growth, other than Needleman's Table 2. In response the Offices provides the following somewhat cryptic statement (page 8, lines 17-20),

> it is well [known?] that PGJ, [and 15-$D^{12,14}PGJ_2$][8] are endogenous activators of peroxisome proliferator activated receptors....[9] Applicant has also admitted that DP receptors [sic **agonists** of the DP receptor?] include PGD2 and its analogs, which in turn include PGJ_2.

The above quotations is the Office's only attempt to link the statements in Needleman's disclosure, which deal with PPAR receptor agonists, to the claims featuring DP receptor agonists.

Apparently the rationale for the rejection boils down to one idea: certain molecules that are DP receptor agonists are also PPAR-γ agonists (although it is not clear which molecules fall into this category). The Office also appears to rely on the idea that certain DP receptor agonists are analogs, metabolites or precursors of certain specific molecules that are PPAR-γ agonists. Specifically, the Office points to **a few specific molecules -- PGJ, and 15-$D^{12,14}PGJ_2$ -- which it says form a "correlation" between the PPAR-γ receptor and the DP receptor**.[10]

The problem is, the very molecules that the Office would use to "establish a correlation" between PPAR-γ agonism and DP receptor agonism are **NOT** (so far as the cited art is concerned) indicated for treating hirsutism. According to the office, the key molecules for making the bridge between DP receptor agonists and PPAR-λ agonists are "prostaglandins of the J_2 series or the PGJ_2 series, such as 15-$D^{12,14}PGJ_2$." Office action page 7, line 21. But those are

---

[8] The compound the Office designates as 15-$D^{12,14}$-PJ_2 is believed to be 15-$D^{12,14}$-PGJ_2.
[9] Citing Corton et al. Annual Rev. Pharmacol. Toxicol. 2000, 40:491-517 p. 498 Table 3 (cited by applicant).
[10] The word "correlation" is the Office's characterization. It is not clear what the word means in this context.

the very PPAR-λ agonists that are NOT indicated to treat hirsutism (at least so far as Needleman Table 2 is concerned).

Stated another way, the logic of the rejection is:

- All PPAR-λ agonists control hair growth
- Some PPAR-λ agonists (which do not themselves control hair growth) are metabolically related to a DP receptor ligand
- Therefore it is obvious that DP receptor agonists control hair growth.

The inconsistency between steps 1 and 2 above, is apparent. The bridge that the Office has tried to construct between PPAR-γ agonism and DP receptor agonism does not exist. **The factual predicates of the rejection** -- both the characterization of what Needleman teaches and the inferences to be drawn from two analogs of PDG2 – are **contradicted by the record**.

B. The legal requirement for a prima facie case of obviousness has not been met

Now that we have reviewed the Office's analysis, the question is whether that analysis is adequate under the law to establish a prima facie case of obviousness.

For claims of a patent to be valid, they must define subject matter that is not obvious (35 U.S.C. § 103) in light of the "prior art," as defined by 35 U.S.C. § 102.

Applicant concedes that the two cited references were publications more than one year before its effective filing date and thus constitute prior art under 35 USC §102(b).

The Office has not rejected any claims for lack of novelty.

The sole art rejection here is based on obviousness, which is governed by 35 U.S.C. §103(a).

More than 40 years ago the Supreme Court provided the framework for analyzing obviousness under § 103. Obviousness must be determined by considering: (1) the scope and content of the prior art, (2) the differences between the prior art and the patent claim, (3) the level of ordinary skill in the pertinent art; and (4) (if there is a prima facie case of obviousness) secondary factors. Graham v. John Deere Co., 383 U.S. 1 (1966).

1. Scope and Content of the Prior art

As to the first of the factual inquiries under the Graham obviousness analysis, the scope and content of the prior art may be established by, among other things, the disclosures of references available at the time of the invention of the claimed subject matter. Relevant references include those in the same field as the claimed invention, as well as those that solve the same problem. In re Nilssen, 851 F.2d 1401, 1403 (Fed. Cir. 1988).

The scope and content of the prior art are reviewed in detail above, including the mischaracterization of Needleman.

2. Differences between the prior art and the claims

In assessing the second factor in the obviousness analysis (the differences between the prior art and the claims at issue), it is first necessary to determine the meaning, and thus the scope, of the claims, as set forth above. See Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 772 (Fed. Cir. 1983), cert. denied, 465 U.S. 1026 (1984).

In this case there does not seem to be any dispute about the meaning of the claim terms. An agonist is a molecule which operates at a receptor in a manner similar to the receptor's natural ligand, and one agonist of the DP receptor is known as 15-deoxy-$\Delta^{12,14}$ PGD_2 or 15d-PDG_2. Many others are listed in the specification as discussed below.

The problem is that the Office does not fairly characterize the prior art and therefore ignores differences between the prior art and the invention in a way that is reversible error. As detailed above, contrary to the factual predicate for the rejection, the art does not teach that every PPAR-γ agonist is indicated for hirsutism. Even less does the art make any connection between hirsutism and DP receptor agonists. In fact when the art (Needleman) lists medical indications for those PPAR-γ agonists which the Office believes are metabolically related to DP receptor agonists, hirsutism is NOT one of the listed indications.

Courts require the Office to be explicit about the differences between the art and the claims to be sure that the Office has engaged in sound analysis. By failing to acknowledge these important differences between the art and the claimed subject matter, the Office has failed to respect this basic requirement imposed both by courts and by Office policy.

3. Level of ordinary skill in the art

The level of ordinary skill in the art, the third factual inquiry, is determined by evaluating the "type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." Custom Accessories v. Jeffrey-Allan Ind., 807 F.2d 955, 962 (Fed. Cir. 1986).

Applicants agree that the level of skill in the art is reasonably high in this case.

4. Secondary factors

Secondary (or objective indicia) if present must be weighed, but where the Office has not established a prima facie case of obviousness, the rejection must be withdrawn even without evidence of secondary factors.

5. The need for sound analysis

In applying the Graham factors, the U.S. Patent and Trademark Office continues to have the burden of establishing a prima facie case that an applicant's claims are obvious. See In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998).

> To reject claims in an application under section 103, an examiner must show an unrebutted prima facie case of obviousness. See *In re Deuel*, 51 F.3d 1552, 1557, 34 U.S.P.Q.2d 1210, 1214 (Fed.Cir.1995). In the absence of a proper prima facie case of obviousness, an applicant who complies with the other statutory requirements is entitled to a patent. See *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

In In re Sang Su Lee, 277 F.3d 1338 (Fed. Cir. 2002), the Federal Circuit held that "[c]ommon knowledge and common sense," even if assumed to derive from the agency's expertise, do not substitute for authority when the law requires authority. Similarly, in In re Zurko, 258 F.3d 1379, 1386 (Fed. Cir. 2001), the Federal Court rejected the Board's arguments of common sense and basic knowledge because they were not based on evidence in the record.

> T]he Board must point to some **concrete evidence** in the record in support of these [obviousness] findings. To hold otherwise would render the process of appellate review for substantial evidence on the record a meaningless exercise. [Emphasis added; Footnote omitted.]

There is great interest in the Supreme Court's opinion in KSR Intern. Co. v. Teleflex Inc., 550 U.S 398 (2007) but KSR has not suddenly made all inventions obvious and it has not removed the requirement that Office provide a sound analytical basis for the obviousness rejection. An important aspect of the obviousness analysis is, and has always been, **the need for a rationale to support the rejection**. The MPEP 2144.02 specifies that, "when an examiner relies on a scientific theory, evidentiary support for the existence and meaning of that theory must be provided". MPEP 2144.03 provides that, "Official notice unsupported by documentary evidence should only be taken by the Office where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known" and "Ordinarily, there must be some form of evidence in the record to support an assertion of common knowledge".

Above we have reviewed the analysis underlying the obviousness rejection. There simply is no concrete evidence that the art would expect **all or even most** PPAR-γ agonists to treat hirsutism. Much less is there any concrete evidence to expect that analogs of the DP receptor agonist PGD_2 would treat hirsutism. **The PGD_2 analogs that Needleman actually lists as having a relationship to DP receptor agonists are not listed as treating hirsutism**. Applicants, through the experiments reported in the specification and discussed below, made the finding that DP receptor agonists reduce hair growth. The art does not include any such teaching.

The cited art does not even support the conclusion that it would have been obvious to try a DP receptor agonist to reduce hair growth. In any event, under these circumstances, the inventive subject matter is not obvious even if it were "obvious to try".

For all of these reasons, the basis for the obviousness rejection is contrary to the facts. The Office has not met the legal standard for establishing obviousness and the rejection must be reversed.

III. The specification as filed enabled the art to practice claims featuring topical administration of DP receptor agonists to reduce hair growth

This is an enablement/overbreadth rejection under 35 U.S.C. §112 ¶1, raised for the first time in the action mailed June 11, 2010. The Office applies the factors the Court approved in In re Wands, 858. F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The Office has misunderstood a key art teaching it relies on and it has ignored important evidence of record bearing on the Wands factors. When that evidence is considered as detailed below, it is clear that the specification enabled those skilled in the art to practice the claimed invention at the time of filing.

A. The breadth of the claims

Claim 1 is representative and is reproduced above. It features controlling hair growth by topical application of a DP receptor agonist. The rejection focuses on the claim term describing the agent used in the method – "agonists of the DP receptor".

The Office notes that the "…genus of agonists of the PGD [DP] receptor…include PDG_2 analogs, derivatives, PGD_2 metabolites and their analogs (citing p. 4, lines 15-16 of the specification)." The claims and the nature of the invention have been discussed above regarding obviousness.

B. The nature of the invention

The Office repeats its analysis from part A. above.

C. The state of the prior art; the level of predictability in the art; -- the art does not teach that BW245C or B246C promote hair growth when administered by themselves.

The Office correctly notes that Applicants have not claimed a new composition of matter. The Office then makes a key finding in support of this rejection (Office Action, page 5, lines 9-15),

> …prior arts [sic art] also teach that some of the agonists of the prostaglandin PD receptors [sic the DP receptor] disclosed by applicant (e.g. BW245C and BW246C) have been used **in a hair growth promoting** agent [citing US2004/0052760 "Michelle [sic Michelet] et al. US2004/052760 at paragraph [0164]].

The office concludes that two DP receptor agonists listed in the Applicants' specification (designated BW245C and BW246C) actually enhance, not reduce, hair growth and, therefore, the state of the art requires a finding that the claim is not broadly enabled. The sole basis for this conclusion is Michelet et al. US2004/052760. This finding -- which is key to the rejection and the only finding under the heading for the "state-of-the-art" and the "level-of-predictability" factors -- is not supported by the evidence as discussed below.

Since the Michelet is central to the rejection, it's important to understand what Michelet actually teaches. Michelet generally concerns encouraging hair growth with inhibitors of one particular enzyme, 15-hydroxyprostglandin dehydrogenase (15PGDH). By inhibiting 15-PDGH such compounds "preserve the endogenous reserves of PGF2α as well as of PGE2" [the substrates which would be degraded by 15PGDH in the absence of the inhibitor] (Michelet [0019]).

The two compounds the Office mentions, BW245C and BW246C, are **not** 15-PGDH inhibitors. Nor is there any reason to think, or cited art teaching, that BW245C or BW246C preserve reserves of PGF2α or PGE2 in any other way. All agree on those facts.

In short, Michelet's teaching about enhancing hair growth by inhibition 15-PDGH is not related to the practice of Applicants' invention. **Nowhere does Michelet suggest that BW245C or BW246C inhibit the 15-PDGH enzyme or that they have any effect on levels of PGFα and PGE2. Nowhere does Michelet suggest that PGFα or PGE2 has anything to do with DP receptor agonism.**

More important, Michelet nowhere suggests that BW245C and BW246C should be administered by themselves, let alone that they would enhance hair growth if administered alone. Rather, in formulating 15-PDGH inhibitors, Michelet proposes a variety of strategies for co-administering a broad range of classes of other compounds. Michelet puts forth a laundry list of strategies which involve agonists of a wide variety of other prostaglandin receptor agonists. Michelet lists the following categories of co-administration strategies:[11]

[11] The paragraph in question is [0164],

> [0164] The composition will additionally contain, for example, at least one compound chosen from prostaglandins, in particular prostaglandin PGE1, PGE2, their salts, their esters, their analogues and their derivatives, in particular those described in [WO] 98/33497, WO 95/11003, JP 97-100091, JP 96-134242,

a) along with the requisite 15-PDGH inhibitors, co-administer PGF2α and PGE2 to increase the amount of these compounds that are present -- as noted, this category has nothing to do with BW245C or BW246C or any other DP receptor agonist;

b) along with the requisite 15-PDGH inhibitors, co-administer compounds that are agonists of the receptors (FP-R or F2-α) that are the natural targets for PGF2α and PGE2 (Michelet [0164]) -- adding agonists of these receptors presumably have the same effect as increasing levels of PGF2α and PGE2; this category has nothing to do with BW245C or BW246C or any other DP receptor agonist;

c) along with the requisite 15-PDGH inhibitors, co-administer agonists of the prostacycline (IP) receptor; this category has nothing to do with BW245C or BW246C or any other DP receptor agonist;

d) along with the requisite 15-PDGH inhibitors, co-administer agonists of the prostaglandin D2 receptor, including BW245C and BW 246C; this of course is the reference the Office relies on; or

e) along with the requisite 15-PDGH inhibitors, co-administer agonists of the receptor for the thromboxanes, A2 (TP); this category has nothing to do with BW245C or BW246C or any other DP receptor agonist.

The rationale for strategies a) and b) are clear and they do not involve BW245C or BW246C. Michelet does not provide any rationale or mechanism for strategies c) -- e), strategy d) being the relevant one for this rejection. Michelet does not report any experiments performed by co-administering any compounds from the above categories, and particularly not from

---

in particular agonists of the prostaglandin receptors. It may in particular contain at least one compound such as the agonists (in acid form or in the form of a precursor, in particular in ester form) of the prostaglandin F2 alpha receptor (FP-R) such as for example latanoprost, fluprostenol, cloprostenol, bimatoprost, unoprostone, the agonists (and their precursors, in particular the esters such as travoprost) of the prostaglandin E2 receptors (EP1-R, EP2-R, EP3-R, EP4-R) such as 17-phenyl PGE2, viprostol, butaprost, misoprostol, sulprostone, 16,16-dimethyl PGE2,11-deoxy PGE1,1-deoxy PGE1, the agonists and their precursors, in particular esters, of the prostacycline (IP) receptor such as cicaprost, iloprost, isocarbacycline, beraprost, the **agonists** and their precursors, in particular the esters, **of the prostaglandin D2 receptor such as BW245C** ((4S)-(3-[(3R,S)-3-cyclohexyl-3-- isopropyl]-2,5-dioxo)-4-imidazolidineheptanoic acid), BW246C ((4R)-(3-[(3R,S)-3-cyclohexyl-3-isopropyl]-2,5-dioxo)-4-imidazolidinehept- anoic acid), the agonists and their precursors, in particular the esters, of the receptor for the thromboxanes A2 (TP) such as I-BOP ([1S-[1a,2a(Z), 3b(1E,3S),4a]]-7-[3-[3-hydroxy-4-[4-(iodophenoxy)-1-buten- yl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid).

category "d)". So there is not even evidence that BW245C or BW246C potentiates hair growth effected by 15-PDGH inhibitors. There is no mechanistic rationale about why they might do so.

Most important, Michelet expresses no belief that BW245C or BW246 C will cause hair growth when administered alone.

Taken as a whole, how would those skilled in the art read this shot-gun, unexplained and untested idea in Michelet to co-administer any of a broad range of substances? The art would understand it for exactly what it is, a invitation to **co-administer** any of a broad range of compounds to determine whether they in fact **potentiate** the hair growth effected by 15-PGDH inhibition.

In sum, the Office makes a key finding regarding these two "Wands" factors (the state of the prior art and the level of predictability in the art) -- i.e., "the prior utility of prostaglandin DP receptors was known to induce the opposite effect of the present invention... (page 5, lines 17-19 of the Office Action)". That finding is a substantial overstatement. Michelet does not have a teaching about the effect of BW245C or BW246C **administered alone**, i.e., in the absence of a 15-PDGH inhibitor. Whatever teaching Michelet has about those compounds is limited to the their effect in **potentiating the 15-PDGH inhibitors** that are central to Michelet's teaching.[12]

On the other side of the balance, examiner ignores extensive teaching art which, when combined with Applicants' hard data and specification, fully enable the art to use DP receptor agonists. These teachings are described below and they include the identity of numerous DP receptor agonists and techniques for identifying and confirming DP receptor agonist activity.

D. The existence of working examples; the quantity of experimentation need to make or use the invention based on the content of the disclosure

On these Wands factors the office acknowledges that the application reports experiments with seven compounds.

---

[12] The examiner believes that Michelet is co-owned with the instant application (see page 5, lines 11-12 of the Office Action). While she does not say so, it may be that she reaches her conclusion about the teaching in Michelet in part on a theory that the Applicant is barred from challenging the extent of the teaching in Michelet because of this alleged co-ownership. Contrary to the Office's speculation, Michelet is owned by Societe L'Oreal, S.A., a competitor of Gillette's parent company, Proctor and Gamble. Neither Applicants nor their assignee bears any responsibility for the authorship of Michelet.

Rather than review those experiments in view of the extensive additional guidance in the application, the office once again relies on a misreading of Michelet (office action page 6, lines 11-15),

> Since the prior art suggests not all agonists of prostaglandin DP receptor are effective for reducing hair growth, and in fact have been used for growing hair, it would be inevitable for a skilled artisan to undergo **undue experimentation** to test the efficacy of the prostaglandin DP receptors which are **not disclosed in working examples of the applicant's specification**. [Emphasis is added.]

In the first place the Office ignores the balance required under Wands and simply rushes to the pre-ordained conclusion that only working examples are "enabled" – a mantra repeated over and over by examiners. MPEP 2164.02[13] makes it clear that the Office must have a reason to impose such a limitation on the claims.

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

The only "reason" given here is Michelet's teaching discussed above. As noted, the Office mischaracterizes Michelet's teaching.

Moreover, the office **ignores** key teachings in the specification. To start with, the Office ignores the substantial knowledge in the prior art (which is referenced in the application as filed) concerning PD agonists. Agonists are defined at page 3, lines 27-30 as compounds that elicits a response that is at least approximately comparable in magnitude to PGD_2. The application teaches the use of specific compounds including:

- PGD_2 (prostaglandin D2);
- PGJ_2 (prostaglandin J2);
- 2-decarboxy-2-hyroxymethyl-deoxy-9,10-didehydro-PGD_2 analogs (taught in US 4,203,924);

[13] Eighth Edition, August 2001, Latest Revision July 2010

- 9-deoxy-9,10-didehydro-prostaglandin D_2 analogs (described in US 4,201,873);
- Trans-delta2-prostaglaindin D_2 derivatives described in US 4,562,204;
- Prostaglandin D_2 analogs described in US 3,878,239;
- 3-oxa-D-prostaglandins described in US 5,700,8356.
- Other prostaglandin D_2 analogs disclosed in EP 0 098 141 and EP0 097 023;
- 11-Deoxy-11-methylene PGD_2,
- 15(R)-15-methyl PGD_2,
- 15(S)-15-methyl PGD_2,
- 15-deoxy-$\Delta^{12,14}$-PGD_2
- 16,16-dimethyl-PGD_2
- 17-phenyl trinor PGD_2,
- 9β-halogen-15-cyclohexyl-prostaglandin,
- 11α-halogen-15-cyclohexyl-prostaglandin,
- ZK118182: Acetic acid, [[(2Z)-4-[(1R,2R,3R,5R)-5-chloro-2-[(1E,3S)-3-cyclohexyl-3-hydroxy-1-propenyl]-3-hydroxycyclopentyl]-2-butenyl]oxy]- (9CI)
- RS93520, Butanoic acid, 4-[(1R,2R,3S,6R)-2-[(3S)-3-cyclohexyl-3-hydroxy-1-propynyl]-3-hydroxybicyclo[4.2.0]oct-7-ylidene]-, (4Z)- (9CI)
- RS93427, Butanoic acid, 4-[(1S,2S,3R,6S)-2-[(3S)-3-cyclohexyl-3-hydroxy-1-propynyl]-3-hydroxybicyclo[4.2.0]oct-7-ylidene]-, (4Z)- (9CI)
- SQ27986, 5-Heptenoic acid, 7-[(1S,2S,3S,4R)-3-[(1E,3S)-3-cyclohexyl-3-hydroxy-1-propenyl]-7-oxabicyclo[2.2.1]hept-2-yl]-, (5Z)- (9CI)
- ZK110841, 5-Heptenoic acid, 7-[(1R,2R,3R,5R)-5-chloro-2-[(1E,3S)-3-cyclohexyl-3-hydroxy-1-propenyl]-3-hydroxycyclopentyl]-, (5Z)- (9CI)
- BW245C, 4-Imidazolidineheptanoic acid, 3-[(3R)-3-cyclohexyl-3-hydroxypropyl]-2,5-dioxo-, (4S)-rel- (9CI)
- BW246C, (4R)-(3-[(3R,S)-3-Cyclohexyl-3-hydroxypropyl]-2,5-dioxo)-4-imidazolidineheptanoic acid
- BW A868C, 4-Imidazolidineheptanoic acid, 3-[(2-cyclohexyl-2-hydroxyethyl)amino]-2,5-dioxo-1-(phenylmethyl)- (9CI)

- L644122, Benzoic acid, 4-[3-[3-[2-(1-hydroxycyclohexyl)ethyl]-4-oxo-2-thiazolidinyl]propyl]- (9CI)
- L644698, Benzoic acid, 4-[3-[3-(3-hydroxyoctyl)-4-oxo-2-thiazolidinyl]propyl]- (9CI)
- 13, 14-Dihydro-15-keto PGD_2,
- Δ^{12}-PGJ_2,
- 15-deoxy-$\Delta^{12,14}$-PGJ_2
- 9,10-dihydro-15-deoxy-$\Delta^{12,14}$-PGJ_2,

In addition, Applicants have conducted experiments showing the art how to use those known compounds and establishing that the compounds, as a class, control hair growth.

The Office tries to minimize the extent of the direction and working examples contained in the specification by simply saying that the "Specification pages 11-13 show in vitro human hair follicle growth assay using seven compounds that are PGD_2 or its analogs (Office action page 6, lines 5-8)."

Apparently the Office refers to Table III, which does in fact list results from seven compounds in a hair follicle growth assay. The Office ignores Table IV, listing five additional compounds.

The Office also ignores the data (Table V) showing that hair growth control effected by DP receptor agonists is dose dependent. The Office also references the hair follicle growth assay as an "in vitro" assay. The assay used to generate the data in Table V involves cell systems and is well accepted. Simply designating it an "in vitro" assay does not justify ignoring it. The specification details the assay at page 11.[14]

---

[14] **Human hair follicle growth assay:**

Human hair follicles in growth phase (anagen) were isolated from face-lift tissue (obtained from plastic surgeons) under dissecting scope using a scalpel and watchmakers forceps. The skin was sliced into thin strips exposing 2-3 rows of follicles that could readily be dissected. Follicles were placed into 0.5 ml William's E medium (Life Technologies, Gaithersburg, MD.) supplemented with 2 mM L-glutamine, 10 μg/ml insulin, 10 ng/ml hydrocortisone, 100 units of penicillin, 0.1 mg/ml streptomycin and 0.25 μg/ml amphotericin B. The follicles were incubated in 24-well plates (1 follicle/well) at 37°C in an atmosphere of 5% CO_2 and 95% air. Compounds are dissolved into dimethyl sulfoxide as 100-fold stock solution. The control hair follicles were treated with dimethyl sulfoxide without prostaglandin. The follicles were photographed in the 24-well plates under the dissecting scope at

At pages 5-8 of the specification, the Applicants provide teachings about formulating the above compounds for topical administration and Examples 1-11 provide 11 different specific topical formulations for the above compounds. At pages 11-13, Applicants provide a detailed assay for experimentally verifying that a particular compound will control hair growth.

Summary

Apart from that misreading of Michelet, there is no analysis of the Wands factors. The Office has not questioned that the art would be well aware of assays to determine whether a compound is an agonist of the DP receptor. For Example, US 5,958,723 discloses assays used to determine whether a compound binds human DP receptor, and whether the compound enhances cAMP production. The specification includes a detailed disclosure of a hair follicle growth asay. There is no question that the art had available to it a large number of compounds that are agonists of the DP receptor. Similarly Applicants do not understand the Office to doubt that it would be routine work to screen to determine which members of a library of novel compounds qualify as DP receptor agonists. Given the highly developed state of the art in November, 2003, there is no question that it would be routine to screen for and find DP agonist compounds in addition to the extensive list of DP agonists that were already known at that time.

Such routine experimentation (even tedious and time-consuming routine experimentation) is not undue experimentation:

> Even accepting that the experimentation required to produce prodrugs and metabolites based on the compound of Formula I would be tedious and time-consuming, the Examiner has not established that it would have been anything other than routine and empirical for one of skill in the art. Ex parte Liu et al., Appeal 2009-015302, Application 10/820,647, Decision of the Board of Interferences and Patent Appeals mailed 9/17/2010.

When the specification is actually reviewed and when Michelet is read as one skilled in the art would read it, analysis of the Wands factors leads to the conclusion that the specification enables the claims. There is no room for deference to the Office where the Office has misread a key reference and where the Office simply ignores key portions of the specification.

---

a power of 10X. Typically, image recordings were made on day 0 (day follicles were placed in culture), and again on day 7. The length of hair follicle was assessed using an image analysis software system. The growth of hair fiber was calculated by the subtracting the follicle length on day 0 from that determined on day 7.

This rejection must be reversed.

The brief fee of $540 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing 00216-0654001.

Respectfully submitted,

Date: 10/26/2010

John W. Freeman, Esq.
Reg. No. 29,066

Customer Number 26163
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

Appendix of Claims

1. A method of reducing mammalian hair growth which comprises

selecting an area of skin from which reduced hair growth is desired; and

applying to said area of skin a dermatologically acceptable composition comprising an agonist of prostaglandin DP-receptor in an amount effective to reduce hair growth.

2. The method of claim 1, wherein said agonist is a prostaglandin D_2 analog.

4. The method of claim 1, wherein said agonist interacts strongly with the prostaglandin DP-receptor.

8. The method of claim 1, wherein said agonist is 15-deoxy-$\Delta^{12,14}$-PGD_2.

29. The method of claim 1, wherein the concentration of said agonist in said composition is between 0.1% and 30%.

30. The method of claim 1, wherein the composition provides a reduction in hair growth of at least 30% when tested in the Human Hair Follicle assay.

31. The method of claim 1, wherein the composition provides a reduction in hair growth of at least 60% when tested in the Human Hair Follicle assay.

32. The method of claim 1, wherein the agonist is applied to the skin in an amount of from 10 to 3000 micrograms of said agonist per square centimeter of skin.

33. The method of claim 1, wherein said mammal is a human.

34. The method of claim 33, wherein said area of skin is on the face of a human.

35. The method of claim 33, wherein the composition is applied to the area of skin in conjunction with shaving.

36. The method of claim 33, wherein said area of skin is on a leg of the human.

37. The method of claim 33, wherein said area of skin is on an arm of the human.

38. The method of claim 33, wherein said area of skin is in an armpit of the human.

39. The method of claim 33, wherein said area of skin is on the torso of the human.

40. The method of claim 1, wherein the composition is applied to an area of skin of a woman with hirsutism.

41. The method of claim 1, wherein said hair growth comprises androgen stimulated hair growth.

42. The method of claim 1, wherein the composition further includes a second component that also causes a reduction in hair growth.

43. A method of reducing mammalian hair growth, which comprises

selecting an area of skin including hair follicles from which reduced hair growth is desired; and

applying to the skin a compound selected from the group consisting of prostaglandin D_2, analogs of prostaglandin D_2, PGJ_2, or an analog of PGJ_2, in an amount effective to reduce hair growth.

44. A method of reducing mammalian hair growth, which comprises

selecting an area of skin including hair follicles from which reduced hair growth is desired; and

applying to the skin a compound that activates DP receptor signal transduction pathway in an amount effective to reduce hair growth.

45. A method of reducing mammalian hair growth, which comprises

selecting an area of skin including hair follicles from which reduced hair growth is desired; and

applying to the skin a compound that inactivates prostaglandin D_2 metabolic pathway in an amount effective to reduce hair growth.

Evidence Appendix

NONE.

Related Proceedings Appendix

NONE.